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# Trisubstituted Isoxazoles from 3,4-Disubstituted-(2*H*)-isoxazol-5-ones

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***Abstract:*** A new trisubstituted isoxazole synthesis, starting from 3,4-disubstituted-(2*H*)-isoxazol-5-ones, is reported

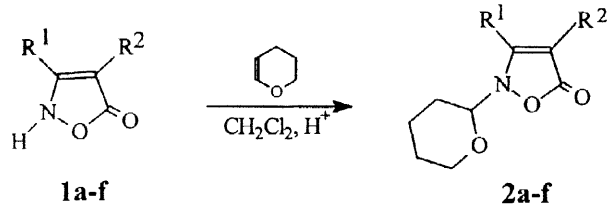

*Keywords:* isoxazoles, protecting groups, lithium compounds, ring transformations

The general synthesis of isoxazoles by reaction of hydroxylamine with 1,3-dicarbonyl compounds was first reported by Claisen in 1888.[1] This classical method provides a convenient preparation of 4-substituted isoxazoles having the same substituent at the 3- and 5-position. For unsymmetrical 1,3-dicarbonyl compounds the possibility of forming two, not easily separable, isoxazoles is a disadvantage.[2]

Continuing our researches on the reactivity of (2*H*)-isoxazol-5-ones,[3] we report here an easy method for the synthesis of trisubstituted isoxazoles starting from 3,4-disubstituted-(2*H*)-isoxazol-5-ones. We have previously reported on the transformation of 3,4-disubstituted-(2*H*)-isoxazol-5-ones into 3,4-disubstituted isoxazoles.[4] To the best of our knowledge, only the synthesis of 5-halo-3,4-disubstituted isoxazoles from the corresponding (2*H*)-isoxazol-5-ones has been reported[5-7].

The reaction of the known (2*H*)-isoxazol-5-ones **1a-f** with 3,4-dihydro-2*H*-pyran, in $CH_2Cl_2$ and in the presence of a catalytic amount of *p*-toluenesulfonic acid, gave the corresponding *N*-protected isoxazolones **2a-f**, in good yield (Scheme 1).

Scheme 1




**1a-f** **2a-f**

| 1,2 | $R^1$ | $R^2$ | 1,2 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **a** | Ph | Et | **d** | Ph | $CH_2Ph$ |
| **b** | Ph | Me | **e** | Me | $C_{16}H_{33}$ |
| **c** | | $-(CH_2)_4-$ | **f** | Ph | $C_8H_{17}$ |

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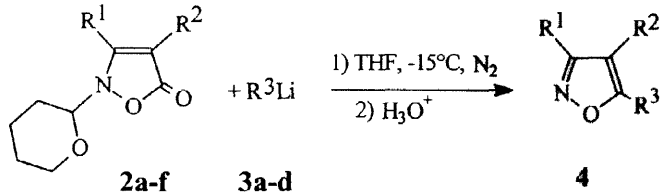
The treatment of compounds **2**, in THF at –15°C, with alkyl and aryl lithium compounds **3** gave, after acidic work-up, the corresponding trisubstituted isoxazoles **4** in very good yield (Scheme 2).

Scheme 2

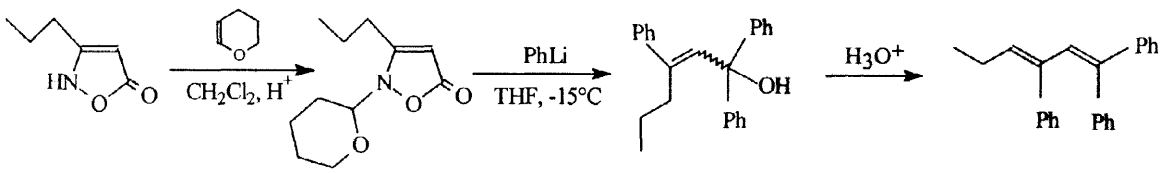



**2a-f** **3a-d** **4**

| 3 | $R^3$ | 4 | $R^1$ | $R^2$ | $R^3$ | 4 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|---|---|---|---|
| **a** | n-Bu | **aa** | Ph | Et | n-Bu | **cd** | | $-(CH_2)_4-$ | Ph |
| **b** | n-Hx | **ac** | Ph | Et | 2-furyl | **da** | Ph | $CH_2Ph$ | n-Bu |
| **c** | 2-furyl | **ad** | Ph | Et | Ph | **db** | Ph | $CH_2Ph$ | n-Hx |
| **d** | Ph | **ba** | Ph | Me | n-Bu | **dc** | Ph | $CH_2Ph$ | 2-furyl |
| | | **bb** | Ph | Me | n-Hx | **ea** | Me | $C_{16}H_{33}$ | n-Bu |
| | | **bc** | Ph | Me | 2-furyl | **ed** | Me | $C_{16}H_{33}$ | Ph |
| | | **cc** | | $-(CH_2)_4-$ | 2-furyl | **fc** | Ph | $C_8H_{17}$ | 2-furyl |
| | | | | | | **fd** | Ph | $C_8H_{17}$ | Ph |

This method did not work for the synthesis of 3,5-disubstituted isoxazoles from 4-unsubstituted (2*H*)-isoxazol-5-ones. These compounds gave the corresponding *N*-protected derivatives in good yield, but the subsequent reaction with lithium derivatives gave products arising from 1,4- and 1,2-additions. From the 3-propyl-(2*H*)-isoxazol-5-one **1g** we have prepared the protected compound **2g**, from which, after treatment with an excess of PhLi, we have obtained in low yield the alcohol **5**, easily transformed into the diene **6** by acidic treatment (Scheme 3).

Scheme 3




**1g** **2g** **5** **6**

## EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a JASCO IR Report 100 instrument, in Nujol mull for solids and as liquid films for oils. $^1$H-NMR spectra were recorded on a Varian Gemini 200 or a Bruker AVANCE DRX 300 spectrometer in $CDCl_3$; chemical shifts are expressed in ppm (δ) relative to TMS, coupling constants (*J*) in Hz. Column chromatography was performed on Kieselgel Merck 60, 0.063-0.2 mm. Evaporation was carried out under vacuum on a rotary evaporator. Compounds **1a**,[8] **1b**,[9] **1c**,[10] **1d**,[11] **1e**,[12] **1f**[13] and **1g**[14] were prepared according to the literature procedure.

*3,4-Disubstituted-2-(tetrahydro-pyran-2-yl)-2H-isoxazol-5-ones* **2**. *General Procedure*.

The (2*H*)-isoxazol-5-one **1** (5 mmol) was dissolved in $CH_2Cl_2$ (30 mL) and then 3,4-dihydro-(2*H*)-pyran (0.66 mL, 7 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After the reported time, the reaction mixture was evaporated and the residue purified by silica gel column chromatography to give:

**2a**, 10 h (hexane-$Et_2O$, 2 : 1) (97%); mp 167-168°C ($Et_2O$); IR 1720, 1620 cm$^{-1}$; $^1$H-NMR δ 1.09 (3H, t, 7.5), 1.25-1.65 (3H, m), 1.80-2.20 (3H, m), 2.30 (2H, q, 7.5), 3.18 (1H, m), 3.86 (1H, m), 4.43 (1H, m), 7.26-7.53 (5H, m); Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 69.99; H, 6.96; N, 5.06.

**2b**, 3 h (hexane-$Et_2O$, 2 : 1) (75%); mp 148°C ($Et_2O$); IR 1718, 1628 cm$^{-1}$; $^1$H-NMR δ 1.25-1.65 (3H, m), 1.70-2.20 (3H, m), 1.88 (3H, s), 3.16 (1H, m), 3.85 (1H, m); 4.45 (1H, m), 7.38-7.57 (5H, m); Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.63; H, 6.58; N, 5.30.

**2c**, 10 h (hexane-$Et_2O$, 2 : 1) (91%); mp 85-86°C (hexane-$Et_2O$); IR 1710, 1630 cm$^{-1}$; $^1$H-NMR δ 1.47-2.17 (10H, m), 2.25 (2H, m), 2.45 (2H, m), 3.48 (1H, m), 3.98 (1H, m), 4.70 (1H, dd, 2.6, 9.8); Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.53; H, 7.70; N, 6.27.

**2d**, 10 h (hexane-$CH_2Cl_2$, 2 : 1); mp 119°C (hexane-$Et_2O$); IR 1718, 1620 cm$^{-1}$; $^1$H-NMR δ 1.33-1.44 (3H, m), 1.80-2.30 (3H, m), 3.18 (1H, m), 3.57 (1H, d, 15.5), 3.67 (1H, d, 15.5), 3.88 (1H, m), 4.49 (1H, dd, 2.5, 10.0), 7.24 (5H,m), 7.46 (5H, m); Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C,75.02; H, 6.34; N, 4.12.

**2e**, 3 h (hexane-$Et_2O$, 3 : 1) (92%); mp 59-60°C (hexane); IR 1708, 1623, 1602 cm$^{-1}$; $^1$H-NMR δ 0.88 (3H, m), 1.24 (26H, m), 1.53 (6H, m), 1.8-2.25 (7H, m), 3.49 (1H, m), 3.98 (1H, m), 4.74 (1H, dd, 2.6, 9.9); Anal. Calcd. for $C_{25}H_{45}NO_3$: C, 73.66; H, 11.13; N, 3.44. Found: C, 73.53; H, 11.18; N, 3.42.

**2f**, 3 h (hexane-$Et_2O$, 3 : 1) (73%); mp 68°C (hexane-$Et_2O$); IR 1725, 1620 cm$^{-1}$; $^1$H-NMR δ 0.85 (3H, m), 1.18 (10H, m), 1.50 (5H, m), 1.80-2.20 (3H, m), 2.24 (2H, m), 3.15 (1H, m), 3.86 (1H, m), 4.42 (1H, dd, 2.6, 10.2), 7.46 (5H, m); Anal. Calcd. for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.85; H, 8.80; N, 3.85.

**2g**, 3 h ($CH_2Cl_2$) (86%); mp 72-73°C (hexane-$Et_2O$); IR 1717, 1570 cm$^{-1}$; $^1$H-NMR δ 1.03 (3H, t, 7.3), 1.45-1.80 (5H, m), 1.85-2.30 (3H, m), 2.47 (2H, m), 3.51 (1H, m), 4.00 (1H, m), 4.80 (1H, dd, 2.6, 9.7), 5.17 (1H, s); Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.38; H, 8.14; N, 6.59.

*Trisubstituted isoxazoles* **4aa, ad, ba, bb, cd, da, db, ea, ed** and **fd.** *General procedure.*

To a solution of compound **2** (2 mmol) in anhydrous THF (7 mL), at –15°C under nitrogen, a solution of the lithium derivative **3** (2.5 mmol) was added. After 5 min at room temperature, the reaction mixture was evaporated, acidified with 2% HCl (25 mL) and extracted with $CH_2Cl_2$ (2 x 20 mL). The organic layer was dried ($Na_2SO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography to give:

**4aa**, (hexane-$Et_2O$, 2 : 1) (95%); oil; IR 1608, 1582 $cm^{-1}$; $^1$H-NMR δ 0.92-1.10 (6H, m), 1.43 (2H, m), 1.72 (2H, m), 2.50 (2H, q, 7.6), 2.74 (2H, t, 7.3), 7.46 (3H, m), 7.60 (2H, m); Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.36; H, 8.41; N, 6.19.

**4ad**, (hexane-$Et_2O$, 2 : 1) (89%); mp 92°C (hexane-$Et_2O$) (reported [13] 93°C).

**4ba**, (hexane-$Et_2O$) (95%); oil; IR 1612, 1560 $cm^{-1}$; $^1$H-NMR δ 0.96 (3H, t, 7.3), 1.40 (2H, m), 1.71 (2H, m), 2.08 (3H, s), 2.74 (2H, t, 7.3), 7.45 (3H, m); 7.66 (2H, m); Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.89; H, 8.01; N, 6.55.

**4bb**, (hexane-$Et_2O$, 10 : 1) (90%); oil; IR 1617, 1560 $cm^{-1}$; $^1$H-NMR δ 0.90 (3H, m), 1.33 (6H, m), 1.68 (2H, m), 2.07 (3H, s), 2.74 (2H, t, 7.4), 7.44 (3H, m), 7.67 (2H, m); Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.77; H, 8.77; N, 5.72.

**4cd**, (hexane-$Et_2O$, 10 : 1) (63%); mp 76°C (hexane-$Et_2O$) (reported[14] 64-65°C).

**4da**, (hexane-$Et_2O$, 10 : 1) (63%); oil; IR 1608, 1590 $cm^{-1}$; $^1$H-NMR δ 0.91 (3H, t, 7.3), 1.34 (2H, m), 1.63 (2H, m), 2.69 (2H, t, 7.3), 3.87 (2H, s), 7.12 (2H, m), 7.24 (3H, m), 7.40 (3H, m), 7.50 (2H, m); Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.35; H, 7.15; N, 4.74.

**4db**, (hexane-$Et_2O$, 10 : 1) (75%); oil; IR 1608, 1590 $cm^{-1}$; $^1$H-NMR δ 0.87 (3H, m), 1.26 (6H m), 1.66 (2H, m), 2.67 (2H, t, 7.4), 3.86 (2H, s), 7.10 (2H, m), 7.24 (3H, m), 7.40 (3H, m), 7.50 (2H, m); Anal.Calcd. for $C_{22}H_{25}NO$: C, 82.72; C, 7.89; N, 4.38. Found: C, 82.62; H, 7.80; N, 4.29.

**4ea**, (hexane-$Et_2O$, 40 : 1) (62%); oil; IR 1618 $cm^{-1}$; $^1$H-NMR δ 0.93 (6H, m), 1.20-1.50 (30H, m), 1.64 (2H, m), 2.20 (3H, s), 2.27 (2H, m), 2.63 (2H, t, 7.3); Anal. Calcd. for $C_{24}H_{45}NO$: C, 79.27; H, 12.47; N, 3.85. Found: C, 79.02; H, 12.33; N, 3.79.

**4ed**, (hexane-$Et_2O$, 10 : 1) (65%); oil; IR 1620, 1582 $cm^{-1}$; $^1$H-NMR δ 0.98 (3H, m), 1.25 (26H, m), 1.56 (2H, m), 2.30 (3H, s), 7.46 (3H, m), 7.67 (2H, m); Anal. Calcd. for: $C_{26}H_{41}NO$: C, 81.40; H, 10.77; N, 3.65. Found: C, 81.22; H, 10.66; N, 3.60.

**4fd**, (hexane-$CH_2Cl_2$, 6 : 1) (86%); mp 51°C (hexane-$Et_2O$); IR 1608, 1580, 1560 $cm^{-1}$; $^1$H-NMR δ 0.86 (3H, m), 1.18 (10H, m), 1.52 (2H, m), 2.71 (2H, m), 7.49 (6H, m), 7.63 (2H, m), 7.74 (2H, m); Anal. Calcd. for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.71; H, 8.20; N, 4.07.

*5-Furan-2-yl-3,4-disubstituted isoxazoles* **4ac, bc, cc, dc** and **fc.** *General procedure.*

Furan (0.29 mL, 4 mmol) was dissolved in anhydrous THF (5 mL) and, at –15°C under nitrogen, 2.5 M

solution of BuLi in hexane (2.5 mmol, 1 mL) was added. After 5 min at –15°C, the compound **2** (1 mmol) was added and the reaction mixture was stirred at room temperature for 5 min. The solvent was then evaporated, 2% HCl (15 mL) added and the mixture extracted with $CH_2Cl_2$ (2 x 15 mL). The organic layer was dried ($Na_2SO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography to give:

**4ac**, (hexane-$Et_2O$, 5 : 1) (96%); mp 76°C (hexane-$Et_2O$); IR 1630, 1608 $cm^{-1}$; $^1$H-NMR δ 1.20 (3H, t, 7.5), 2.80 (2H, q, 7.5), 6.57 (1H dd, 1.8, 3.5), 6.91 (1H, bd, 3.3), 7.49 (3H, m), 7.63 (3H, m); Anal. Calcd. for $C_{15}H_{13}NO_2$ : C, 75.30; H, 5.48; N, 5.85. Found: C, 75.15; H, 5.40; N, 5.79.

**4bc**, (hexane-$Et_2O$, 10 : 1) (90%); mp 78-79°C (hexane-$Et_2O$); IR 1620 $cm^{-1}$; $^1$H-NMR δ 2.37 (3H, s), 6.57 (1H, dd, 1.8, 3.3), 6.89 (1H, bd, 3.3), 7.45-7.72 (6H, m); Anal. Calcd. for: $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.52; H, 4.88; N, 6.12.

**4cc**, (hexane-$Et_2O$, 3 : 1) (68%); mp 76°C (hexane ) ( reported[15] 73-74°C).

**4dc**, (hexane-$Et_2O$) (84%); mp 90°C (hexane); IR 1612 $cm^{-1}$; $^1$H-NMR δ 4.16 (2H, s), 6.53 (1H, dd, 1.8, 3.5), 6.83 (1H, bd, 3.0), 7.11-7.55 (11 H, m); Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.59; H, 4.96; N, 4.60.

**4fc**, (hexane-$CH_2Cl_2$, 3 : 1) (88%); oil; IR 1634, 1538 $cm^{-1}$; $^1$H-NMR δ 0.87 (3H, m), 1.22 (10H, m), 1.57 (2H, m), 2.76 (2H, m), 6.57 (1H, dd, 1.8, 3.4), 6.90 (1H, m), 7.49 (3H, m), 7.62 (3H, m); Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.86; H, 7.68; N, 4.32.

*1,1,3-Triphenylhex-2-en-1-ol* **5** *from* **2g**.

To a solution of compound **2g** (422 mg, 2 mmol) in anhydrous THF (10 mL), at –15°C under nitrogen, 1.8 M solution of PhLi in cyclohexane-ether 70/30 (4.5 mL, 8.1 mmol) was added. After 5 min at room temperature, the reaction mixture was evaporated, acidified with 2% HCl and extracted with $Et_2O$ (2 x 20 mL). The organic layer was dried ($Na_2SO_4$) filtered and evaporated. The residue was purified by silica gel column chromatography (hexane-$Et_2O$, 10 : 1) to give pure compound **5**, oil; IR 3525, 3420, 1610, 1580 $cm^{-1}$; $^1$H-NMR δ 0.64 (3H, t, 7.2), 1.13 (2H, m), 2.46 (1H, s, exchange with $D_2O$), 2.49 (2H, m), 6.43 (1H, s), 7.20-7.60 (15H, m); Anal. Calcd. for $C_{24}H_{24}O$: C, 87.76; H, 7.36. Found: C, 87.96; H, 7.02.

*1,1,3-Triphenylhexa-1,3-diene* **6** *from compound* **5**.

To a solution of compound **5** (328 mg, 1 mmol) in ethanol (20 mL) 9% HCl (5 mL) was added. The reaction mixture was heated under reflux for 5 min. The solvent was then evaporated, the residue diluted with water (10 mL) and extracted with $Et_2O$ (2 x 20 mL). The organic layer was dried ($Na_2SO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane) to give pure compound **6**, oil; IR 1642, 1580 $cm^{-1}$; $^1$H-NMR δ 0.81 (3H, t, 7.4), 2.00 (2H, m), 5.76 (1H, t, 6.2), 6.67 (1H, bs), 7.07-7.40 (15H, m); Anal.Calcd. for $C_{24}H_{22}$: C, 92.86; H, 7.14. Found: C, 92.76; H, 7.20.

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